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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/487,851	01/19/2000	Robert J. Levy	7600-20CT (CHOP-0013)	3653

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EXAMINER
LI, QIAN J

ART UNIT	PAPER NUMBER
1632	29

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/487,851	Applicant(s) LEVY ET AL.	
	Examiner Q. Janice Li	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/1/02 & 12/3/02* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4,5,16,17,30-38 and 65-70* is/are pending in the application.

4a) Of the above claim(s) *69 and 70* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4,5,16,17,30-38 and 65-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 December 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1☐ Certified copies of the priority documents have been received.

2☐ Certified copies of the priority documents have been received in Application No. _____ .

3☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/3/02 has been entered and assigned as Paper No. 28.

The amendment after final Office action filed on 11/1/2002 has been entered and assigned as paper No. 25. Claims 1-3, 6-15, and 18-29 have been canceled. Claims 69 and 70 are newly submitted. Claims 4, 5, 16, 17, 30-38, and 65-70 are pending.

Newly submitted claims 69 and 70 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the original claimed invention is drawn to a method of alleviating a disease or disorder in an affected animal cell comprising locally delivering a vector to the cell, whereas the newly submitted claims are drawn to an invention for identifying a candidate therapeutic gene comprising identifying and selecting a gene. Inventions are distinct if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case, the different methods achieve different functions, have different method steps, and use different materials and test criteria in the process. The

gene selection and identification process is not required in the therapeutic process, and in vivo administration of a vector is not used in the process of gene identification.

Since applicant has received several actions on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 69 and 70 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

In paper No. 25, applicants indicated that they have followed the examiner's suggestion by adding new claims 69 and 70. While during the interview with the applicant and applicants' representative, in light of the delineation by one of the inventors regarding the nature of the invention, the Examiners did suggest that the applicants might consider presenting claims drawn to a different invention provided the specification has a proper support for it. However, the Examiners did not suggest adding claims drawn to a different invention to the current application.

Claims 4, 5, 16, 17, 30-38, and 65-68 are under current examination.

Claim Objections

Claims 4, 5, 16, 17, 30-38, and 65-68 are objected to under 37 CFR 1.75(c), as being of improper dependent from canceled claims. Applicant is required to amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. For purpose of compact prosecution, the claims would be interpreted as they depend from the original claim 1 in this Office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4, 5, 16, 17, 30-38, and 65-68 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In Paper #25, applicants indicated that their invention provides a ""yin and yang" approach, where one cellular response associated with a disease/disorder is "countered" by administering a therapeutic gene product associated with an opposite cellular response. They go on to argue that importantly, knowledge of the mechanism underlying a particular disease process does not figure in implementing the methodology of the present invention, accordingly, the quantity of experimentation necessary to make and use the claimed invention would not be undue.

The arguments have been carefully considered but they are not persuasive for reasons of record advanced in paper Nos. 11 and 22, and following.

The statement, "knowledge of the mechanism underlying a particular disease process does not figure in implementing the methodology of the present invention", is contradictory to the teachings of the specification, because the specification teaches the basis of using the "yin and yang" approach depended on the knowledge for the

mechanism underlying re-entrant arrhythmias. The specification teaches, "a number of mechanisms have been investigated to explain atrial arrhythmias, and are the basis for the conventional therapeutic approach" (2nd paragraph, page 2), "As described herein, reverse gene therapy can be used to appropriately alter myocardial sites involved in mechanistic events leading to re-entrant arrhythmias because use of pathologic mutants of ion channel proteins defeats tachyarrhythmic conduction circuits and achieves, a 'biotech ablation' of such arrhythmias" (paragraph bridging pages 10 and 11). There are times when the knowledge of the mechanism underlying a particular disease process does not figure in implementing a treatment strategy when a method has been reduced to practice and a surprising result contrary to the expected outcome based on the common knowledge was found. However, this is not the case in the instant specification. The specification has not reduced to practice to show that the administration of a reverse gene therapy vector has indeed alleviated any disease or disorder with or without knowing the mechanism underlying the disease. The claimed invention is based on the knowledge of the skilled in the art, and proposes a creative use of a defective gene.

Applicants further indicate that the invention as claimed are now limited to treating or alleviating with a defective HERG gene, a symptom (re-entrant artrial flutter) associated with abnormalities of a cardiac tissue, and the Examiner has not propounded a reasonable basis for urging that the mutant HERG will not influence biophysical function in vivo.

In response, it is noted that the remaining claims have not been presented in such a way, as they are limited to treating a particular disease with a particular mutant gene. Moreover, a claim drawn to a method of treatment would be evaluated by that standard. As indicated in paper Nos. 11 and 22, the Office cited teachings of *Sanguinetti and Kagan et al* to specifically address why the effect of mutant HERG on the dog model of re-entrant atrial flutter is not predictable until the actual effect is shown. Such unpredictability could further be seen in a post-filing publication (*Bradley et al*, J Clin Invest 1999 Mar;102;889-96), where the overexpression of the *normal* HERG gene in ventricular myocytes *suppresses* cardiac hyperexcitability, whereas the applicants have predicted and showed that a *defective* HERG would do so at least *in vitro*.

The reasoning for placing reasonable doubt on *in vivo* effects of a defective HERG with regard to the *treatment* of a cardiac disease was given in paper No. 22, wherein from the teaching of the skilled artisan, the discovery of a dysfunctional gene and delivery of such gene for compensation has not brought a therapeutic effect in gene therapy for diabetes and cystic fibrosis:

In the supplemental Response paper #21, applicants submitted additional data, demonstrating expression and membrane-localization of both the wide-type and mutant channels in HEK293 cells and stem cells *in vitro*, that the mutant Q9E MiRP channel has influenced biophysical function of the K+ channel in normal cells *in vitro*, and that 15% of cardiac myocytes were transfected in pig right atrial samples *in vivo*. These additional data, however, has not provide sufficient enabling disclosure for the scope of the claims because the biophysical influence of the mutant gene has not been shown *in vivo* or in cells with abnormal K^+ channel, and has not translated to any therapeutic benefit in alleviating any disease or disorder in any affected animal as instantly claimed. It remains to be the position of the Office that the *in vitro* and *in vivo* data are not well correlated in gene therapy art as taught by *Boucher et al* (J Clin Invest 1999 Feb; 103:441-5) for example, which has been cited in the previous Office action and will be

reiterated here, "DESPITE AN IMPRESSIVE AMOUNT OF RESEARCH IN THIS AREA, THERE IS LITTLE EVIDENCE TO SUGGEST THAT AN EFFECTIVE GENE-TRANSFER APPROACH FOR THE TREATMENT OF CF LUNG DISEASE IS IMMINENT. THE INABILITY TO PRODUCE SUCH A THERAPY REFLECTS IN PART THE LEARNING CURVE WITH RESPECT TO VECTOR TECHNOLOGY AND THE FAILURE TO APPRECIATE THE CAPACITY OF THE AIRWAY EPITHELIAL CELLS TO DEFEND THEMSELVES AGAINST THE PENETRATION BY MOIETIES, INCLUDING GENE-THERAPY VECTORS, FROM THE OUTSIDE WORLD." Applicants are reminded of numerous factors complicating gene therapy, which have not been shown to be overcome by routine experimentation or resolved using animal models or *in vitro* studies. These factors include the fate of the DNA vector itself (volume of distribution, rate of clearance, the fraction taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the host immune response etc.), the *in vivo* consequences of altered gene expression and protein function, the stability of the mRNA produced, the amount and stability of the protein produced, the compartmentalization and secretory fate of the protein within the cell. These factors differ dramatically based on the vector used, the protein being produced, the organs and tissues involved and the disease being treated. (*Eck et al*, pg81, col 2, paragraph 3, and page 82, col. 1, paragraph 2). The unpredictability of gene therapy is also caused by the lack of knowledge in understanding the etiology and mechanism of a disease. For example, *Alton et al* (Lancet 1999 Mar; 353:947-54) teach after successful attempt to partially correct chloride channel biophysical activity *in vivo*, "WE WERE UNABLE TO SHOW ANY CORRECTION OF THE INCREASED SODIUM ABSORPTION", "AT PRESENT, IT IS NOT CLEAR WHETHER BOTH SODIUM AND CHLORIDE ABNORMALITIES NEED TO BE CORRECTED FOR CLINICAL BENEFIT; NOR IS IT CLEAR WHETHER ONLY THE LATTER REQUIRES CORRECTION, AND TO WHAT DEGREE IT NEEDS TO BE RESTORED TO PREVENT OR TREAT THE LUNG DISEASE", "IF THE SODIUM ABNORMALITY ALSO REQUIRES CORRECTION FOR CLINICAL BENEFIT, GENE THERAPY FOR CYSTIC FIBROSIS IS SOME WAY SHORT OF SUCH A TARGET". (paper No. 22, pages 6-7)

The teaching of *Alton et al* also illustrated the importance of knowledge of the mechanism underlying a disease is to the success of implementing gene therapy strategy. Perhaps, the teaching of *Mazhari* (Cir Res 2002:90:842-3) more specifically addresses the correlation of manipulating cell biophysical properties *in vitro* and correcting a disease phenotype. In *Mashari* reference, a computational model showed that "in order to achieve the same degree of QT-interval shortening without causing a higher degree of dispersion of repolarization, transgene transduction has to be homogeneous across the ventricular wall" (left column, page 843). This should also be the case for correction of re-entrant artrial flutter, wherein one of the many requirements

is the ability to transfect a significant population of cells at a significant level for correction of the disease phenotype.

In conclusion, the Office relied on the combined teachings of the prior- and post-filing date art to provide a reasonable basis to show that one skilled in the art could not practice the invention without undue experimentation, because "WHEN CONSIDERING THE FACTORS RELATING TO A DETERMINATION OF NON-ENABLEMENT, IF ALL THE OTHER FACTORS POINT TOWARD ENABLEMENT, THEN THE ABSENCE OF WORKING EXAMPLES WILL NOT BY ITSELF RENDER THE INVENTION NON-ENABLED." "LACK OF A WORKING EXAMPLE, HOWEVER, IS A FACTOR TO BE CONSIDERED, ESPECIALLY IN A CASE INVOLVING AN UNPREDICTABLE AND UNDEVELOPED ART." (MPEP 2164.02, 03) Therefore, it is evident that at the time of the invention, the gene therapy practitioner, while acknowledging the significant potential of gene therapy, still recognized that such therapy was neither routine nor accepted, and awaited significant development and guidance for its practice. Therefore, it is incumbent upon applicants to provide sufficient and enabling teachings within the specification for such therapeutic regimen. Therefore, it is applicants duty to disclose each aspect of the invention in such a way as MPEP indicated, "THE DISCLOSURE CORRESPONDING TO EACH ASPECT OF THE INVENTION MUST BE ENABLING TO A PERSON SKILLED IN EACH RESPECTIVE ART. (MPEP 2106.B.2)

For reasons of record and those set forth above, the instant specification fails to meet the enablement requirement.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4, 5, 16, 17, 30-38, and 65-68 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are vague and indefinite because they depend from canceled claims and the recited limitations in these claims lack antecedent basis.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Patent Examiner
Art Unit 1632

QJL
February 24, 2003